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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/808,827	02/28/97	GUNZBURG W	GSF97-01A

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EXAMINER	
BRUSCA, J	
ART UNIT	**PAPER NUMBER**
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/808,827	Applicant(s) Gunzburg et al.
	Examiner John S. Brusca	Group Art Unit 1636

☒ Responsive to communication(s) filed on *9/21/98* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 5, 7-26, and 28-30* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 5, 7-26, and 28-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _ __

☐ Interview Summary, PTO-413

☑ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an International application filed on 9/1/95. It is noted, however, that applicant has not filed a certified copy of the International application as required by 35 U.S.C. 119(b).

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark on 9/2/94. It is noted, however, that applicant has not filed a certified copy of the foreign application as required by 35 U.S.C. 119(b).

3. The Applicants stated in the Amendment filed 9/21/98 that the Office Action requested a certified copy of the claimed International and foreign applications to comply with 35 U.S.C. § 120, however the request was concerning claims for priority under 35 U.S.C. § 119.

4. The Applicants have provided a copy of the Demand of International Application PCT/EP95/03445, which establishes that a chain of copendency exists between the instant application and the claimed International application as required under 35 U.S.C. § 120.

Specification

5. The objection to the specification in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

Claim Objections

6. Claims 22-24 and 30 are objected to because of the following informalities:

Claims 22-34 recite "Recombinant retroviral particle" in claim 22, and should be amended to recite --A recombinant retroviral particle-- in claim 22.

Claim 30 recites "Recombinant retroviral particle" and should be amended to recite --The recombinant retroviral particle--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The rejection of claims 1-27 under 35 U.S.C. § 112, first paragraph in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

8. The rejection of claims 1-27 under 35 U.S.C. § 112, second paragraph in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 5, 7-26, and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 5, 7, 8, and 16 are indefinite because a comma does not appear after the term "promoters" which results in an indefinite member of the recited group. The rejection would be overcome by amending claim 5 to insert a comma after "promoters".

12. Claim 7 is indefinite because commas do not appear after the terms "promoters" in line 7 and "gland" in line 9 which results in indefinite members of the recited group. The rejection would be overcome by amending claim 7 to insert a comma after "promoters" and "gland".

13. Claim 9 is indefinite because a comma does not appear after the term "virus" in line 7 which results in an indefinite member of the recited group. The rejection would be overcome by amending claim 9 to insert a comma after "virus" in line 7.

14. Claims 11 and 12 are indefinite because a comma does not appear after the phrase "cytokine genes" which results in an indefinite member of the recited group. The rejection would be overcome by amending claim 11 to insert a comma after "cytokine genes".

15. Claim 12 is indefinite because a comma does not appear after the phrase "hypoxanthine phosphoribosyl transferase (HPRT) gene" which results in an indefinite member of the recited group. The rejection would be overcome by amending claim 12 to insert a comma after "hypoxanthine phosphoribosyl transferase (HPRT) gene".

16. Claim 21 is indefinite because a comma does not appear after the phrase "regulatory sequences and promoters" which results in an indefinite member of the recited group. The rejection would be overcome by amending claim 21 to insert a comma after "regulatory sequences and promoters".

17. Claim 30 recites the limitation "of a retroviral vector kit according to claim 29". There is insufficient antecedent basis for this limitation in the claim. The rejection would be overcome by amending claim 30 to recite --with the retroviral particle of claim 29-- and deleting the phrase "with the retroviral vector according to claim 29,."

18. Claims 18 and 19 recite the limitation "The retroviral vector system according to claim 17". There is insufficient antecedent basis for this limitation in the claim. The rejection would be overcome by amending the claims to recite --The kit of claim 17--.

19. Claims 1, 5, 7-26, and 28-30 are indefinite for recitation of the phrase "target cell type restricted" because it is not clear what type of restriction the claim is drawn to. The Applicants have pointed to basis in the specification for the phrase at pages 9 and 15, but the phrase does not appear at those locations, nor is the phrase defined in the specification. The rejection would be overcome by amending the claims to be drawn to regulatory elements and promoters that are target cell specific in their expression as in originally presented (now cancelled) claim 6.

20. Claim 7 recites the limitation "said target cell specific regulatory elements and promoters". There is insufficient antecedent basis for this limitation in the claim. The rejection would be overcome by amending claim 7 to recite --wherein the regulatory elements and promoters--.

21. Claim 13 is indefinite for recitation of the phrase "wherein at least one of said coding sequences is a retroviral sequence coding for a retroviral protein, and the retroviral sequence is

altered or at least partially deleted" because it is not clear how an altered or partially deleted sequence can encode a protein. The rejection would be overcome by amending the claim to recite --wherein at lease one of said coding sequences is an altered or partially deleted retroviral gene.

22. For the purpose of examination, the claims have been assumed to incorporate the suggested amendments.

Claim Rejections - 35 USC § 102

23. The rejection of claims 1, 3, 4, 9, 11, 12, 14, 17, 18, 20, 22, 23, 24, 25, and 27 under 35 U.S.C. 102(b) as being anticipated by Faustinella et al. in light of Panganiban '84 and Scarpa et al. is withdrawn in view of the Amendment filed 9/21/98.

Claim Rejections - 35 USC § 103

24. The rejection of claims 1, 10, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Price et al. in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

25. The rejection of claims 1, 10, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Price et al. in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

26. The rejection of claims 1, 3, 4, 15, 17, 20, 21, 22 26, and 27 under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Longmore et al. and Kay et al. in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment filed 9/21/98.

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

28. Claims 1, 5, 7-9, 11-13, 16-25, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al.

Claim 1 is drawn to a retroviral vector comprising a substitution of a portion of the 3' U3 region with a heterologous DNA fragment that is expressed in a target-cell-specific manner. Claim 5 is drawn to the retroviral vector of claim 4 further limited to a heterologous

DNA fragment that is a regulatory element or a promoter. Claim 7 is drawn to the vector of claim 5 further limited to a target sell specific regulatory element and promoter selected from the group consisting of Whey Acidic Protein specific regulatory elements and promoters, Mouse Mammary Tumor Virus specific regulatory elements and promoters, beta lactoglobulin and casein specific regulatory elements and promoters, pancreas specific regulatory elements and promoters, lymphocyte specific regulatory elements and promoters, and mouse mammary tumor virus specific regulatory elements and promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland. Claim 8 is drawn to the vector of claim 5 further limited to regulatory elements and promoters that regulate the expression of a coding sequence of the vector. Claim 9 is drawn to the retroviral vector of claim 1 further limited to an LTR derived from a virus selected from the group consisting of murine leukemia virus, mouse mammary tumor virus, Murine sarcoma virus, simian immunodeficiency virus, human immunodeficiency virus, human T cell leukemia virus, feline immunodeficiency virus, feline leukemia virus, bovine leukemia virus, and mason-pfizer monkey virus. Claim 11 is drawn to the retroviral vector of claim 1 further limited to comprise a coding sequence consisting of marker genes, therapeutic genes, antiviral genes, antitumor genes, or cytokine genes. Claim 12 is drawn to the vector of claim 11 further limited to a marker or therapeutic gene selected from the group consisting of beta-galactosidase gene, neomycin gene, Herpes Simplex Virus thymidine kinase gene, puromycin gene, cytosine deaminase gene, hygromycin gene, secreted alkaline phosphatase gene, guanine

phosphoribosyl transferase gene, alcohol dehydrogenase gene, and hypoxanthine phosphoribosyl transferase gene. Claim 13 is drawn to the vector of claim 1 comprising an altered retroviral gene. Claim 16 is drawn to the vector of claim 5 further limited to regulatory elements regulatable by trans acting molecules. Claim 17 is drawn to a kit comprising the retroviral vector of claim 1 and a packaging cell line that packages the vector of claim 1. Claim 18 is drawn to the kit of claim 17 further limited to a packaging cell line that expresses retroviral proteins not expressed by the vector of the kit. Claim 19 is drawn to the kit of claim 17 further limited to a packaging cell selected from the group consisting of psi-2, psi-crypt, psi-AM, GP+E86, PA317, and GP+envAM-12. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in humans or animals or cultured cells of humans or animals. Claim 21 is drawn to the method of claim 20 further limited to comprise genes, regulatory sequences, or promoters. Claim 22 is drawn to a retrovirus produced by the kit of claim 17. Claim 23 is drawn to a retroviral provirus produced by infecting cells with the retrovirus of claim 22. Claim 24 is drawn to mRNA of the provirus of claim 23. Claim 25 is drawn to RNA of the retrovirus of claim 1. Claim 28 is drawn to a packaging cell. Claim 29 is drawn to the retrovirus produced by the vector of claim 1. Claim 30 is drawn to the retrovirus produced from the kit of claim 29.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and theNae I site used to construct the

vectors of figure 2. pS3 also comprises a stop codon in the gag region. In figure 2, Faustinella et al. shows modified pS3 vectors in which the luciferase reporter gene operably linked to a rous sarcoma virus promoter or the hygromycin resistance gene operably linked to a herpes simplex thymidine kinase promoter has been inserted in the polylinker region. The luciferase gene is a well known marker gene and the thymidine kinase gene is a well known antitumor gene. Faustinella et al. shows in the Materials and Methods section that the viral vectors were packaged in the GP+AM12 cell line, which expresses retroviral proteins not expressed by the retroviral vector, such as the gag protein, in its function as a packaging cell line. The packaging amd expression of pS3 in NIH-3T3 cells detailed in Faustinella et al. shows the mRNA and RNA of the retroviral vector were produced during infection of cultured animal cells. Faustinella et al. does not show heterologous DNA that is expressed in a target cell specific manner, or regulatable elements that are explicitly regulated by trans acting molecules, or a BAG vector, or a pharmaceutical comprising a retroviral vector.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows a retroviral vector comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 murine retroviruses. Couture et al. shows in the abstract that after packaging the substituted U3 region appears at the 5' LTR and serves as a promoter for vector genes, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within

retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. by use of the LTR regions of Mee et al. or Couture et al. because Couture et al. shows that insertion of a promoter region in a deleted 3' U3 region of a retroviral vector results in the expression of vector genes under the control of the inserted promoter in a cell type specific manner, and that internal promoters may not function properly in a retroviral vector, and that target cell specific retroviral vectors have utility in gene therapy protocols, and because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types. It would have been further obvious to use packaging cell lines PA317 and GP&E86 because Couture et al. shows that they may be used to package retroviral vectors.

29. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above, and further in view of Price et al.

Claim 10 is drawn to the vector of claim 1 further limited to a vector based on a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

30. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above, and further in view of Panganiban et al. '84 in view of Scarpa et al.

Claim 14 is drawn to the vector of claim 1 comprising an altered or partially deleted sequence involved in integration of retroviruses.

Scarpa et al. shows in figure 2 and the discussion on page 851 that a mutation of the start codon in the gag region to a stop codon (as in the vector pS3 of Faustinella) results in the absence in translation of the pol gene. Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral

genome to form a provirus. Therefore, the stop codon mutation in pS3 affects sequences involved in the integration of retroviruses.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a retroviral vector with a mutation in sequences involved in integration because Scarpa et al. and Panganiban et al '84 show that the vector of Faustinella et al. comprises such a mutation, and Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above make obvious the invention of claim 1.

31. Claims 15 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above, and further in view of Longmore et al. in view of Kay et al.

Claim 15 is drawn to the vector of claim 1 comprising a DNA fragment homologous to a cellular sequence. Claim 26 is drawn to a pharmaceutical comprising the retrovirus of claim 22.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Faustinella et al. in view of Couture et al. in view of Mee et al. as applied to claims 1, 5, 7-9, 11-13, 16-25, and 28-30 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal. Regarding the limitation in claim 15 to a vector comprising a DNA fragment homologous to a cellular sequence, the erythropoietin receptor gene of Longmore et al. or the factor IX gene of Kay et al. teach such a sequence in a retroviral vector.

32. Applicant's arguments filed 9/21/98 have been fully considered but they are not persuasive. The Applicants state that Couture does not show cell specific promoters, however in Table 3, Couture et al. shows chimeric LTR promoters that are cell type specific. The Applicants state that the degree of specificity of the promoters of Couture et al. are not adequate to meet the limitations of the claimed invention, but the Applicants have not pointed to any quantitative element to the degree of specificity in the claimed invention that would prevent the application of Couture et al. in the rejections detailed above. Further, Mee et al. teaches an MMTV promoter that is taught in the specification on page 11. The promoter of Mee et al. would therefore provide a promoter that reads on the claimed promoter.

Conclusion

33. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

34. Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. For routine submissions the FAX number is (703) 308-4242. For FAX transmissions in cases in which the Examiner has been notified by phone to expect the transmission, the FAX number is (703) 305-7939. In such cases please call the Examiner at (703) 308-4231 at the time of transmission to expedite delivery of the fax. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6 (d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or

applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, Ph.D., can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John S. Brusca, Ph.D.

Examiner

George C. Elliott, Ph.D.
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